

Claims

1. A method for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia, which comprises:
contacting a cell with a candidate therapeutic agent, or administering a candidate therapeutic agent to an organism;
determining whether expression of any of the following genes is altered in the cell or organism in response to the candidate therapeutic agent: PARG; OLR1; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRCFS1; UQCRC2; UQCRCB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2; FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1; and
identifying the candidate as a potential therapeutic agent if expression of one or more of the genes is altered.

2. A method according to claim 1, wherein it is determined whether expression of any of the genes is altered by comparing the expression level of the gene or genes in the presence and absence of the candidate therapeutic agent.

3. A method according to claim 1 or 2, wherein the candidate is identified as a potential therapeutic agent if expression of one or more of the following genes is increased: PARG; OLR1; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRCFS1; UQCRC2; UQCRCB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2; or expression of one or more of the following genes is decreased: FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-

REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

4. A method according to claim 1 or 2, wherein the candidate is identified as a potential therapeutic agent if expression of the majority of the following genes is altered in response to the therapeutic agent: PARG; VDAC2; OLR1; ARPC3; UQCRRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

5. A method according to claim 4, wherein the candidate is identified as a potential therapeutic agent if expression of the majority of the genes is altered in the following ways: an increase in expression of: PARG; VDAC2; OLR1; ARPC3; UQCRRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; a decrease in expression of: FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

6. A method according to any preceding claim, wherein it is determined whether expression of the gene or genes is altered in the prefrontal cortex of the organism.

7. A method according to any preceding claim, wherein the organism is a mouse or a rat.

8. A method according to any preceding claim, wherein the organism is an animal model for a neuropsychiatric disorder.

9. A method according to any preceding claim, wherein the cell is a neuronal cell.

10. A method according to any preceding claim, wherein a microarray is used to determine whether expression of the gene or genes is altered.

11. A method according to any preceding claim, which further comprises determining the side effects caused by administration of the candidate if it is identified as a potential therapeutic agent.

12. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a modulator of expression of any of the genes specified in claim 1 by: providing a system capable of expressing any of the genes specified in claim 1; maintaining the system under conditions for expression of the gene in the presence and absence of a candidate modulator of expression of the gene; and determining the expression level of the gene in the presence and absence of the candidate modulator.

13. A screening assay according to claim 12, which comprises screening for an upregulator of expression of any of the following: PARG; OLR1; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRCFS1; UQCRC2; UQCRCB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

14. A screening assay according to claim 12, which comprises screening for a downregulator of expression of any of the following: FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

15. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a regulator of the activity of any of the proteins encoded by the genes specified in claim 1 by: contacting the protein with a candidate regulator and determining the activity of the protein in the presence and absence of the candidate regulator.

16. A screening assay according to claim 15, which comprises screening for an enhancer or activator of the activity of any of the following proteins: PARG; OLR1; ARPC3; DNCLI1;

PPM1A; ATP1F1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRCB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

17. A screening assay according to claim 15, which comprises screening for an inhibitor of the activity of any of the following proteins: FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

18. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a regulator of the interaction of any of the proteins encoded by the genes specified in claim 1 with a binding partner required for the biological effect of the protein by: contacting the protein with the binding partner in the presence of a candidate regulator, and determining binding of the protein to its binding partner in the presence and absence of the candidate regulator.

19. A screening assay according to claim 18, which comprises screening for an enhancer of the interaction of any of the following proteins with a binding partner required for the biological effect of the protein: PARG; OLR1; ARPC3; DNCLI1; PPM1A; ATP1F1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRFS1; UQCRC2; UQCRCB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

20. A screening assay according to claim 18, which comprises screening for an inhibitor of the interaction of any of the following proteins with a binding partner required for the

biological effect of the protein: FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

21. A screening assay to identify a potential schizophrenia therapeutic agent for the prevention, treatment, or amelioration of schizophrenia which comprises screening for a binding partner of any of the proteins encoded by the genes specified in claim 1 by: contacting the protein with a sample comprising a candidate binding partner, and determining whether the candidate binding partner binds to the protein.

22. Use of any of the following proteins or nucleic acids in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia:

(i) proteins encoded by the following genes: PARG; OLR1; ARPC3; DNCLI1; PPM1A; ATPIF1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRCFS1; UQCRC2; UQCRB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2; FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1; or ii) nucleic acid encoding any of the proteins of (i) above.

23. Use of a regulator of expression of any of (i) of claim 22 in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

24. Use of a binding partner of any of (i) or (ii) of claim 22 in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

25. Use of an expression vector comprising nucleic acid encoding any of (i) of claim 22 in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.

26. Use of a cell or cell line expressing nucleic acid encoding any of (i) of claim 22 in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.
27. Use according to claim 26, wherein the cell is a neural cell.
28. Use according to claim 26, wherein the cell is an oligodendrocyte.
29. A recombinant mouse in which expression of a gene encoding any of (i) of claim 22 is altered compared with expression of the corresponding gene in normal mice.
30. A recombinant mouse according to claim 29 in which expression of two or more of the genes is altered.
31. A recombinant mouse according to claim 29 or 30, which is a knockout mouse for the gene or genes.
32. Use of a recombinant mouse according to any of claims 29 to 31 as an animal model for schizophrenia.
33. Use of a mouse according to any of claims 29 to 31, or cells obtained or derived from the mouse, in a screening assay to identify a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia.
34. Use of a binding partner of nucleic acid encoding any of the genes specified in claim 1, or of a protein encoded by any of the genes specified in claim 1, to determine the level of expression of the gene.
35. Use according to claim 34 in a method of diagnosing whether a subject has, or is at risk of developing schizophrenia.
36. A method of diagnosing whether a subject has, or is at risk of developing schizophrenia, which comprises determining the level of any of the proteins of (i) of claim 22, or the expression level of a gene encoding any of the proteins of (i) of claim 22, in a

biological sample obtained from the subject, or in a sample derived from a biological sample obtained from the subject.

37. A method according to claim 36, wherein the expression level of the majority of the following genes, or the levels of the majority of the proteins encoded by the following genes is determined: PARG; VDAC2; OLR1; ARPC3; UQCRRFS1; DNCLI1; PPM1A; ATP1F1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COLSA1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

38. A method according to claim 36 or 37, wherein the biological sample comprises a peripheral tissue or cell type in which the level of the protein, or the expression level of the gene, correlates with the level of the corresponding protein, or the expression level of the corresponding protein, in the prefrontal cortex.

39. A method according to claim 38, wherein the peripheral tissue or cell type comprises a blood cell.

40. A method according to claim 39, wherein the blood cell is a macrophage, a monocyte, a lymphocyte, an erythrocyte, a platelet, a leukocyte (either a neutrophil, an eosinophil, or a basophil; a lymphocyte, or a monocyte).

41. A method of prevention, treatment, or amelioration of schizophrenia which comprises increasing the level or activity of any of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration: PARG; OLR1; ARPC3; DNCLI1; PPM1A; ATP1F1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRRFS1; UQCRC2; UQCRCB; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2.

42. A method of prevention, treatment, or amelioration of schizophrenia which comprises reducing the level or activity of any of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration: FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

43. A method of prevention, treatment, or amelioration of schizophrenia which comprises increasing the level or activity of the majority of the following proteins in the brain (in particular the prefrontal cortex) of a subject in need of such prevention, treatment, or amelioration: PARG; VDAC2; OLR1; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; and reducing the level or activity of the majority of the following proteins in the brain (in particular the prefrontal cortex) of the subject: FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

44. A microarray for use in a method for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia according to any of claims 1 to 11, or in a method of diagnosis according to any of claims 36 to 40.

45. A microarray according to claim 44, which is a gene chip comprising a plurality of different probes capable of hybridising to nucleic acid expression products, or nucleic acid derived from nucleic acid expression products, of the majority of the following genes: PARG; VDAC2; OLR1; ARPC3; UQCRFS1; DNCLI1; PPM1A; ATPIF1; GLRX2; TIMM17A; IDH3B; ARG2; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; SLC25A4; FLJ13611; HIRIP5; COX7A2; COX5A; TAC1; UQCRH; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; HMGCL; TXNL2; SOD3; BCAT2; MT1X.

46. Use of a microarray according to claim 44 or 45 in a method for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia, or in a method of diagnosis of schizophrenia.

47. A kit for use in a method for identifying a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia according to any of claims 1 to 11, or in a method of diagnosis according to any of claims 36 to 40, the kit comprising means for detecting expression products, or nucleic acids derived from nucleic acid expression products, of a plurality of the following genes: PARG; OLR1; ARPC3; DNCLI1; PPM1A; ATP1F1; TIMM17A; DNAJA1; SST; NEUROD6; ICAP-1A; FLJ23251; KCNK1; FLJ13611; HIRIP5; TAC1; MAGEH1; C13orf12; EBNA1BP2; DIRAS2; MPPE1; OAT; OAZIN; OAZ2; ARG2; ATP6V1B2; ATP6IP2; ATP6V1C1; ATP5J; ATP5G3; ATP5L; ATP5C1; ATP5F1; ATP5A1; NDUFA5; NDUFA6; NDUFAB1; NDUFB3; NDUFB6; NDUFB5; NDUFB1; NDUFS4; NDUFA4; NDUFC2; NDUFB4; UQCRH; UQCRRFS1; UQCRC2; UQCRR; UQCRC2; COX7A2; COX7B; COX5A; COX17; COX11; COX7CP1; COX7BP1; HCCS; SLC25A4; VDAC2; VDAC1P; VDAC3; LDHB; LDHA; IDH3B; IDH3A; HMGCR; GLRX2; FBS1; WFS1; AMT; CLN3; ACOX1; G6PD; GCDH; COL5A1; NY-REN-24; TXNL2; SOD3; BCAT2; ALDH4A1; PYCR1; MT1X; MT1L; MT1G; MT1H; MT2A; MT1E; MT1F; DDAH2; AMT; HMGCL; EPHX1.

48. A kit according to claim 47, which further comprises one or more of the following:

- i) instructions for using the detecting means for diagnosis, prognosis, or therapeutic monitoring;
- ii) a labelled moiety for detecting the detecting means;
- iii) a solid phase to which the detecting means is immobilised;
- iv) a predetermined amount of an isolated expression product of one or more of the genes for use as a standard, or control;
- v) a label or insert indicating regulatory approval for diagnostic, prognostic or therapeutic use as appropriate.

49. A method for identifying a schizophrenia patient, or a patient suspected of having schizophrenia, who is likely to respond to a therapeutic treatment that alters the level or activity of any of the proteins specified in (i) of claim 22, the method comprising: determining the level of expression of any of the genes encoding the proteins specified in (i) of claim 22 in a patient, or in a biological sample obtained from the patient; and identifying the patient as being likely to respond to the therapeutic treatment if the level of expression of the gene or genes is altered compared to a normal subject.

50. A method for selecting a participant in a clinical trial to determine the effectiveness of a potential therapeutic agent for the prevention, treatment, or amelioration of schizophrenia,

the method comprising: determining the level of expression of any of the genes encoding the proteins specified in (i) of claim 22 in a candidate participant, or in a biological sample obtained from the candidate participant; and selecting the candidate for the clinical trial if the level of expression of the gene or genes is altered compared to a normal subject.